lesions of the right side. According to Lebert,[106] while 30 per cent. of these patients die of tuberculosis, it is not necessarily of the lungs, and when in the lungs the cause is not to be attributed to anemia, but to the unequal and abnormal character of the circulation. The lungs receive their blood supply, as Norris[107] points out, from the bronchial arteries. The pulmonary tuberculosis is usually miliary in type (Fox[108]).

Frommolt[109] states that disease of several valves is not uncommon in connection with this lesion, but otherwise seldom occurs. Meisenberg[110] found only 20 in 182 instances of cardiac disease in pulmonary tuberculosis, in which the aortic and mitral valves were simultaneously affected. Jaccoud has observed many instances of tricuspid insufficiency with venous pulse, and Osler[111] mentions the frequency with which the venous pulse is observed in pulmonary tuberculosis. Other observers have made little or no note of it. Tricuspid insufficiency may be a source of great danger in benign chronic cases with sclerosis.

To summarize, it may be said that pulmonary stenosis is always the primary disease, mitral insufficiency and aortic insufficiency usually the primary. The most frequent cardiac lesion secondary to pulmonary tuberculosis in patients up and about is mitral stenosis. Pulmonary tuberculosis occurs more frequently in patients with pulmonary stenosis than in any other form of cardiac disease. Mitral insufficiency is associated with pulmonary tuberculosis more often than any other form of valvular disease, but aortic insufficiency is not very much less frequent. Aortic stenosis is very rarely associated with pulmonary tuberculosis, and pulmonary stenosis is infrequent in pulmonary tuberculosis. Involvement of several valves simultaneously is rare in these cases.

DIAGNOSIS. The heart plays an important part in the diagnosis of pulmonary tuberculosis, and in many instances it is impossible to arrive at any definite conclusion. Marshall[112] reports several instances at the Johns Hopkins Hospital in which cardiac disease was diagnosticated as pulmonary tuberculosis and the error discovered at autopsy. Three instances have come under my notice in which a similar diagnosis was made and in which, after a most careful study, pulmonary tuberculosis could be excluded.

TREATMENT. The treatment of the various forms of valvular heart disease, occurring in connection with pulmonary tuberculosis, differs in no way from that ordinarily employed in cardiac disease. Moderate elevations, not over 2000 feet, are said by Anders[113] to be the best for patients with valvular disease, but if well compensated they often do well at greater elevations. Patients should be fully warned against overexertion, for they have even less reserve force than the ordinary patients with only cardiac disease, and slight efforts may produce signs of non-compensation in both systems, rendering them much more susceptible to secondary infection (Bohland[114]). The treatment of the rapid heart action and cardiac weakness in pulmonary tuberculosis differs but slightly from that ordinarily employed. Digitalis and strophanthus are of little avail. Arsenic, strychnine (in large doses), an ice-bag over the precordium, carbonic acid baths, rubs, absolute rest at first, and carefully regulated exercises relegated chiefly to those muscles which throw little or no stress upon the muscles of the thorax, are all of value. Nitroglycerin may give marked relief. Excitement of any sort should be avoided, and it is wise to refrain from the use of alcohol and tobacco and to use coffee in moderation, if at all. Burton-Fanning[115] has pointed out the value of restriction of food, and in some cases it is wise to omit milk for a time. Flatulency must be rigorously combated and the diet should be rich in easily digested proteids. Palpitation of the heart should be treated by rest and the ice-bag, but bromides and valerian may be required.

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[106] Loc. cit.

[107] Loc. cit.

[108] Diseases of the Lungs and Pleura, London, 1891, p. 547.

[109] Loc. cit.

[110] Loc. cit.

[111] Principles and Practice of Medicine, 1905, p. 333.

[112] Loc. cit.

[113] Loc. cit.

BACILLUS COLI COMMUNIS: THE CAUSE OF AN INFECTION CLINICALLY IDENTICAL WITH TYPHOID FEVER.

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Cases of infection clinically identical with typhoid fever have been caused by Bacillus fæcalis alcaligenes, the paratyphoid and paracolon bacilli (Bacillus paratyphosus, types A and B), Bacillus enteritidis, and Bacillus psittacosis. The close biological relationship of these members of the typhoid-colon group (the Typhaceæ, as Loeffler has designated them recently) and the fact that the paracolons are more nearly related to Bacillus coli than to Bacillus typhosus naturally lead to the suspicion that some strains of Bacillus coli also might be capable of causing the typhoid symptom complex. Though there is increasing evidence of variability, and even mutation, of type among the Typhaceæ, a discussion of this phase of the typhoid problem does not come properly within the scope of our paper.

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[114] Handb. d. chron. Lungenschw., 1904, p. 694.

[115] Open-air Treatment of Pulmonary Tuberculosis, Chicago, 1905, p. 103.

Our attention was first directed to the question of systemic infection by the colon bacillus pursuing a typhoid-like course in 1903, when Buxton and one of us recovered colon bacilli from the blood of two cases in Bellevue Hospital which were considered clinically as examples of mild typhoid fever. These cases were reported briefly on a former occasion:

CASE I.—A. F., butcher's helper, entered Bellevue Hospital in the service of Dr. Thompson, August 15, 1903, the eighth day of his illness. He had been swimming daily in the East River. For a week he had suffered from general weakness, frontal headache, pain in the stomach and legs, bad taste in the mouth, and loss of appetite, but in spite of these symptoms had continued at work washing beef tongues in a damp cellar. There had been no vomiting or diarrhœa.

On admission the patient's tongue was coated and tremulous. The spleen was not palpable. About two dozen rose spots were found upon the chest and abdomen. The general appearance of the patient suggested mild typhoid fever. Fresh rose spots appeared on August 17, but by the 20th all the spots had disappeared. The temperature on admission was 100.4° F; pulse, 96. Thereafter the temperature gradually fell and reached normal on the twelfth day of the disease. The patient's serum was tested against the typhoid bacillus on the tenth and twelfth days, microscopically in dilution of 1 to 100, both times with negative results after two hours. Unfortunately the reaction of the serum against the colon bacillus was not tested. On the tenth day of the disease 10 c.c. of blood, taken from a vein at the elbow, contained a colon bacillus in pure culture. August 30, after twelve days of normal temperature, a relapse occurred. During the relapse the temperature rose to a maximum of 101° F. The duration of the relapse is unknown, since on September 14, thirty-eight days after admission, the patient insisted on leaving the hospital with a pulse of 120 and a temperature of 99.5° F.

CASE II.—B. McM. Occupation, housework. Entered Bellevue Hospital August 14, 1903, in the service of Dr. Thompson, complaining of severe general headache, dry cough, pain in the back and sides, loss of appetite, and constipation. She had a temperature of 101.4° F. and a pulse of 100. A clinical diagnosis of mild typhoid fever was made. On the sixth day of illness her serum, in dilution of 1 to 100, was negative microscopically to the typhoid bacillus after two hours. Two days later her blood was found to contain a colon bacillus in pure culture. But the following day her serum gave a positive Widal reaction at 1 to 100. The reaction against Bacillus coli was not tested.

According to present standards, the data concerning Case II are too meager to permit our drawing any conclusion regarding it. We are unable to determine whether the case should be considered as one of primary systemic infection with a colon bacillus, exhibiting a group reaction against the typhoid bacillus, or whether to look upon the presence of Bacillus coli in the blood as a secondary invasion. The former seems the more likely when one considers the small number of patients whose blood has contained Bacillus coli communis during life, and the very infrequent association of Bacillus typhosus and Bacillus coli in the blood of typhoid cases.

Case I, on the other hand, meets the requirements more fully; that is, (1) it was clinically mild typhoid fever, (2) Bacillus coli communis was obtained in pure culture from the blood, and (3) the serum reaction was negative to the typhoid bacillus as late as the last day of the fever in the primary attack. It would have added to the completeness of the data if the patient's serum had been tested against several strains of Bacillus coli, but this was not done. With these cases in our possession, a search of the literature for similar ones was undertaken.

In 1902 Fox recovered a colon bacillus from the blood of a case which resembled typhoid fever clinically. The serum of the patient gave a positive Widal reaction on the thirty-second day of the disease, though it had previously been negative. Therefore, as in Case II above, the true nature of the infection was doubtful.

In the same year Burch wrote, under the title of "Colon Bacillus Infection," that for ten years he had seen in his practice cases of fever, lasting from seven to ten days, which were ushered in by malaise, a gradual rise of temperature to a maximum of 103° to 104° F. by the third or fourth day, diarrhœa, or, less frequently, constipation. The tongue was dry and often coated. Sometimes there was mild delirium; there was always more or less headache. Tympanites occurred in some cases. The whole clinical picture was that of typhoid fever. The leukocytes were diminished in all cases. The urine was always acid and many times swarmed with motile organisms resembling Bacillus typhosus. The diazo reaction was, as a rule, well marked. The Widal reaction, made daily (dilution approximately 1 to 5), was absent in every case throughout its course, but the serum reacted promptly to the organism obtained under aseptic conditions from the bladders of the patients. This organism responded to all the cultural tests for Bacillus coli communis. This remarkable series of cases was observed in Baldwinsville, New York. While the nature of the infection cannot be accepted as proved, the cases appear to have been what the author considered them, examples of colon bacillus infection pursuing the course of typhoid fever.

In 1903 three papers appeared upon this subject. Evans and Sailer reported the case of a negro who, on February 12, suddenly became weak and dizzy. Next day he had diarrhœa, loss of appetite, and gastric disturbances. The spleen was palpable. Rose spots were present. The disease ran the course of typical typhoid fever. The temperature became normal on March 6. A relapse occurred which lasted to the 16th. The leukocytes on February 15 numbered 5900; February 17, 10,480; March 9, 7000. The diazo reaction was positive in the first part of the illness. The serum tests upon which the diagnosis rests must be given in detail: Against Bacillus typhosus the reaction was positive at 1 to 10 on five occasions, while it was negative at higher dilutions. Against Bacillus paratyphosus (four strains), the reaction was incomplete at 1 to 10 on the twentieth day of the disease, but it was positive at 1 to 10 on the forty-third day of the disease. Against Bacillus coli communis (Pasteur Institute culture), the reaction was complete in forty-five minutes at 1 to 100 on the twentieth day. On the forty-third day, the reaction was complete at 1 to 150 in one hour, partial at 1 to 200 and 250 in one and a half hours (no increase later), and negative at 1 to 300 and 1 to 400 after twenty-four hours. The case, therefore, appears to have been caused by a colon bacillus.

A. Jacoby, of New Orleans, reported a case which he considered especially interesting because it resembled typhoid fever so closely: A laborer, aged fifty years, was working on a railroad in Texas when he was taken ill. He had drunk any water he could get. There had been no diarrhœa. The temperature on admission to hospital was 101° F.; pulse rapid. The abdomen was distended. The spleen was much enlarged. Rose spots were present. No malarial organisms found. The Widal reaction was negative four times (dilutions and days not stated). Rose spots and the urine were examined for Bacillus typhosus with negative results. Bacillus coli communis was present in the urine in large numbers. After admission the temperature did not rise above 102° F., and in a week began to decline. On the sixteenth day, however, double lobar pneumonia developed, the temperature rose suddenly to 104° F., and death followed. At autopsy, the small intestine was congested throughout its extent, but Peyer's patches were not involved.

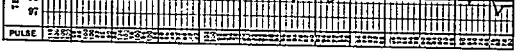
Bauermeister reported the case of a man, aged thirty-five years, from whose blood he obtained Bacillus coli communis in pure culture on several occasions; he regarded the case clinically as typhoid-like in its course. Similar attacks recurred over a period of one and one-half years, when one of the patient's testicles had to be amputated because of an abscess which contained Bacillus typhosus. Bauermeister suggests that the original colon bacillus had changed its biological characters probably as the result of long residence in the body. This case seems to us to belong with the colon bacillus septicemias rather than in the typhoid group which we are discussing.

In 1904 Widal and Lemière reported two cases, which they state resembled typhoid fever, and from whose blood they recovered colon bacilli. As their second case showed multiple abscesses of the kidney at autopsy, it cannot be included in the present series. Their third case occurred in a man, aged thirty-five years, who was taken ill suddenly five days before admission to the hospital with violent abdominal pain, repeated chills, and vomiting. He had almost constant headache and complete insomnia after the onset. There was no epistaxis or diarrhœa. The temperature on admission was 103.5° F.; pulse 90. There was marked abdominal distention. No rose spots. Spleen voluminous. Violent intestinal peristalsis. Heart, lungs, and liver normal. The abdominal pain and tenderness disappeared. Diazo reaction negative. Serum, negative to the typhoid bacillus. The patient's illness lasted from December 12 to December 21. He was discharged from the hospital December 24. On December 18 a colon bacillus was obtained in pure culture from 3 c.c. of blood. December 24, the patient's serum agglutinated his own bacillus at 1 to 30.

These are the only cases we have been able to find, reported as cases of systemic infection by the colon bacillus, pursuing the course of typhoid fever, which will bear analysis.

In the fall of 1905 we were fortunate enough to have the privilege of studying the following case:

Case III.—G. K., aged twenty-nine years, entered Bellevue Hospital October 4, in the service of the late Dr. Loomis. He had been in Central America for a year and a half, where he contracted malaria and yellow fevers. Early in July he spent eight days in Jamaica, *en route* to New York, where he has remained since August 24. During this time he has been well. The present illness dates from September 30, when he felt feverish. He waked next morning with a headache, mainly frontal and occipital; pain in the muscles of the neck on moving the head, and pain in the right knee and arm. Walking was difficult. In spite of these symptoms, the patient went to his office, where he remained until afternoon. On the way home he felt very weak. When he got into bed, he had a chill, lasting twenty minutes, followed by sweating. The headache



Temperature chart of Case III (G. K.).

continued, and pains developed in the back. Three days after the first chill he had another (October 3) lasting ten minutes. His head and hands became very hot, but he did not sweat. October 4 he felt so weak that he decided to remain in bed. His bowels had not moved since October 1. For several days he had had a dry, hacking cough. In the afternoon, when he entered the hospital, he was chilly and suffered from nausea and vomiting.

Physical Examination. The patient is a well-nourished, well-developed man. Face flushed, skin dry, but in good condition. Tongue large, flabby, coated, and tremulous. Heart and lungs normal. Arteries not thickened. Slight abdominal distention. Slight tenderness in left upper quadrant of abdomen. Liver normal. Spleen not palpable. A few rose spots on the abdomen. The clinical picture is that of mild typhoid fever.

Subsequent History. October 5, headache and abdominal pain all night. Slept about two hours. Fresh crop of rose spots. The spots continued to appear at intervals until the 16th. Slight bleeding when the patient blew his nose. From the 6th to the 9th the patient complained chiefly of vague abdominal pain and headache.

October 9. Conjunctivæ and skin slightly icteric.

October 10. Pain in right hypochondrium (heretofore the pain was not localized). Marked jaundice. Tenderness over gall-bladder. Spleen percusses large, but cannot be felt.

October 11. Jaundice deeper. Tenderness over gall-bladder more marked. Nausea. Severe frontal headache.

October 12. Gall-bladder exquisitely tender. Spasm of overlying muscles. Patient brighter.

October 14. Gall-bladder palpable. Extends one and three-fourth inches below free border of ribs.

October 16. Gall-bladder less tender. Jaundice beginning to clear up.

Thereafter the jaundice gradually disappeared, the gall-bladder receded, and tenderness was developed only on deep pressure. This tenderness persisted, however, until October 27, and for months afterward the patient had a sense of discomfort on bending over. The patient was discharged from the hospital as cured on November 17.

Cytological Examinations of the Blood. October 4. Leukocytes, 5000; polynuclears, 62 per cent.; lymphocytes, 24 per cent.; large mononuclears, 8 per cent.; transitionals, 4 per cent. No malarial organisms.

October 5. Leukocytes, 6000; polynuclears, 77 per cent.; lymphocytes, 14 per cent.; large mononuclears, 8 per cent.; eosinophiles, 1 per cent.

October 9. Leukocytes, 6400; polynuclears, 45 per cent.; lymphocytes, 29 per cent.; large mononuclears, 6 per cent.; transitionals, 18 per cent.; eosinophiles, 5 per cent.; mast cells, 0.3 per cent.

October 10. Leukocytes, 8000; polynuclears, 66 per cent.; lymphocytes, 20 per cent.; large mononuclears, 10 per cent.; transitionals, 2 per cent.; eosinophiles, 4 per cent.

Two blood cultures in broth were made October 5 and 9, but both proved negative (Buxton).

Three rose spots were examined bacteriologically with negative results (Buxton).

The urine was examined bacteriologically twice and found negative (Buxton, Warren).

The feces were examined three times for Bacillus typhosus or any of the intermediates, and also found negative (Norris, Buxton).

AGGLUTINATION REACTIONS.[1] AGAINST BACILLUS TYPHOSUS.

October 9, 10, 13, 14, 16, 18, 19:
- Microscopically, in dilution of 1 to 50, negative after two hours.
- Macroscopically, in dilution of 1 to 100, negative after twenty-four hours.

October 21:
- Microscopically, in dilution of 1 to 50, negative after two hours.
- Macroscopically, in dilution of 1 to 100, negative after twenty hours.
- Macroscopically, in dilution of 1 to 200, negative after twenty hours.

October 23:
- Microscopically, in dilution of 1 to 50, negative after two hours.
- Macroscopically, in dilution of 1 to 100, negative after twenty hours.
- Macroscopically, in dilution of 1 to 200, negative after twenty hours.
- Macroscopically, in dilution of 1 to 400, negative after twenty hours.

October 24:
- Microscopically, in dilution of 1 to 50, negative after two hours.
- Macroscopically, in dilution of 1 to 200, negative after twenty hours.
- Macroscopically, in dilution of 1 to 20, negative after twenty hours.

AGAINST BACILLUS PARATYPHOSUS (TYPES A AND B).

October 14:
- Macroscopically, in dilution of 1 to 10, positive after twenty hours.

October 18 and 19:
- Macroscopically, in dilution of 1 to 100, negative after twenty hours.

October 21:
- Macroscopically, in dilution of 1 to 100, negative after twenty hours.
- Macroscopically, in dilution of 1 to 200, negative after twenty hours.

October 23:
- Macroscopically, in dilution of 1 to 100, negative after twenty hours.

October 24:
- Macroscopically, in dilution of 1 to 200, negative after twenty hours.
- Macroscopically, in dilution of 1 to 20, negative after twenty hours.

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[1] The dilutions stated are dilutions of the serum before admixture with the suspensions of bacilli—the final dilutions, therefore, would be twice as high.

AGAINST BACILLUS COLI (STRAIN A).

October 14:
Macroscopically, in dilution of 1 to 20, positive after twenty hours.
October 18 and 19:
Macroscopically, in dilution of 1 to 100, positive after twenty hours.
October 21:
Macroscopically, in dilution of 1 to 200, positive after twenty hours.
October 23:
Macroscopically, in dilution of 1 to 400, positive after twenty hours.
October 24, 26, and 28:
Macroscopically, in dilution of 1 to 200, positive after twenty hours.
October 30 (strains A and B):
Macroscopically, in dilution of 1 to 200, positive to A after twenty hours
negative to B after twenty hours.
November 1:
Macroscopically, in dilution of 1 to 100, positive to A after twenty hours.
negative to B after twenty hours.

November 15, the serum in dilution of 1 to 100 was tested against seventeen strains of Bacillus coli, including strains A and B previously used.

The reactions were positive with strains 2, 6, 13, and A.

December 29, the serum no longer agglutinated any strain of Bacillus coli in dilutions of 1 to 100 and 1 to 20.

All of the reactions above noted were end-reactions—tests with more dilute serum proving negative.

While we are aware that we have not proved *beyond doubt* (through our failure to recover the colon bacillus from the blood) whether G. K.'s. infection, was local (that is, a colon bacillus cholecystitis) or general, we are convinced that we have proved that the disease was not caused by Bacillus typhosus or any of the intermediates. The case was considered clinically to be mild typhoid fever by all who saw him, including the late Dr. Loomis and Dr. Thompson. Nevertheless, to forestall criticism, it will be well to discuss the clinical differential diagnosis.

The various clinical possibilities seem to have been: (1) Clinical typhoid fever, complicated by cholecystitis. (2) Primary cholecystitis. (3) Tuberculosis. (4) Sepsis. (5) Pyelitis.

The condition of the urine throughout the disease excludes pyelitis.

The course of the disease and the subsequent history exclude sepsis and tuberculosis (the patient was not lost sight of until the fall of 1907).

There remain only the two varieties of cholecystitis, catarrhal and suppurative. Suppurative cholecystitis may be excluded for the same reasons as sepsis. As against a primary catarrhal cholecystitis caused by the colon bacillus, we base the clinical diagnosis of a typhoid-like fever upon the following facts: mode of onset with the gradually developing malaise, initial chills, slight bronchitis, slight epistaxis(?), persistent headache, appearance of rose spots on the fifth day of the disease, the course of the disease, the emaciation, and the phenomena of convalescence. Leukopenia, with a low polynuclear count, was present until the day after the cholecystitis became evident clinically. The leukocytes then rose to 8000 and the polynuclears from 45 per cent. to 66 per cent. Though there had been previously vague abdominal pains, these are not uncommon in typhoid fever. Definite tenderness over the gall-bladder did not develop until the day following the subicteric tinging of the conjunctivæ and skin. We are very positive in this statement, because for years it has been our habit to examine daily the gall-bladder region of all patients in the wards suffering from typhoid fever. From all of these considerations we feel justified in thinking that the case of G. K. was clinically typhoid fever, complicated by cholecystitis.

In order to make this study as complete as possible, we have sought during the last three years to obtain the serum of cases suffering from a colon bacillus cholecystitis for the study of its agglutination reactions, but unsuccessfully. We have also written to prominent surgeons to obtain such data, but none of them could furnish the desired information. The literature is silent upon this point. The development of immune bodies for various strains of Bacillus coli in cases of cholecystitis caused by this bacillus offers an interesting and important field for study.

Though it is well established that Bacillus coli may enter the blood during life, only a limited number of cases have been reported in which this fact has been demonstrated by blood culture. Most recent writers on localized colon bacillus infections, for example, of the gall-bladder and of the kidney and its pelvis, recognize the systemic blood stream as one of the channels of infection (Lenhartz, Lockwood, Brewer). While in most of these cases it is probable that the bacillus is only transiently in the blood, Lenhartz and Schmeidemandel have reported cases in which the bacillus has been obtained by blood culture.

A limited number of cases of colon bacillus septicemia have been reported (Bertelsmann and Mann, Lenhartz, Sittman and Barlow, Albarran, Libman, De Gennes and Hartmann, Hitschmann and Michel, Stern, Stadelmann and Wolff-Eisner, Fehling, Blackader and Gillies).

With the possibility of the entrance of the colon bacillus into the blood during life proved, it seems to us that it need excite no surprise that some strains of this bacillus in view of their close resemblance to some of the paracolons, may cause under certain conditions a disease clinically identical with typhoid fever. Buxton and one of us have suggested that even Bacillus typhosus is incapable of causing typhoid fever unless it develops in the general lymphatic system, including the spleen and bone-marrow, and thence invades the blood, where it is destroyed in large numbers. Localized infections with Bacillus typhosus do not cause typhoid fever. Lentz thinks that the same conditions of infection obtain in the typhoid-like types of paratyphoid infection. While there is no direct evidence to offer, from analogy it is probable that when a colon bacillus causes the symptoms of typhoid fever, the distribution of the bacillus in the body is the same as in the case of typhoid and paratyphoid infections.

DISCUSSION OF THE AGGLUTINATION REACTIONS FOR BACILLUS COLI. The blood examinations in Cases I and II of the Bellevue Hospital series have been noted in the clinical report. The presence of Bacillus coli in blood taken from a vein leaves no doubt as to the bacteremia, and we feel inclined to accept this as evidence that this bacillus was the cause of the infection. No tests for immune bodies (agglutinins) were carried out.

In Case III, G. K., blood taken from a vein on two occasions proved sterile, and the supposition that Bacillus coli communis was the cause of the infection is based upon the facts that immune bodies (agglutinins) for a certain strain of Bacillus coli were found in the blood during the febrile period and were not found after recovery, and that the same strain of Bacillus coli was not agglutinated by many other sera in high dilution, thus fulfilling our own ideas of the diagnostic value of agglutination reactions and coinciding with the results of Klieneberger.

	Oct. 10, 1905, 1-50 to 1-100.	Oct. 12, 1-100.	Oct. 14, 1-100.	Oct. 21, 1-200.	Oct. 23, 1-400.	Oct. 24, 1-400.	Oct. 20, 1-100.	Oct. 28, 1-200.	Oct. 30, 1-200.	Nov. 1, 1-100.	Nov. 15, 1-100.	Dec. 20, 1-100 to 1-20.
Bacillus typhosus.	—	—	—	—	—	—	..	..	..	..	—	—
Bacillus paratyphosus A and B.	..	..	—	—	..	..	..	..	..	..	—	—
Bac. coli A.	..	..	++	+++	+++	+++	+++	+++	+++	+++	+	—
Bac. coli B.	..	..	—	—	..	..	..	..	—	—	—	—
Bac. coli No. 2, No. 6, No. 13.	..	..	..	..	..	..	..	..	..	..	+	+
Bacillus coli, 12 strains.	..	..	..	..	..	..	..	..	..	..	—	—

Dilutions refer to the diluted serum; final mixtures were twice the serum diluted.

Agglutination tests in Case III gave the following results: October 10 and 12, tests against Bacillus typhosus were negative in dilutions 1 to 50 and 1 to 100. October 14, the serum diluted 1 to 100 was tested against Bacillus typhosus, Bacillus paratyphosus (A and B), and one strain (A) of Bacillus coli, and the reaction for strain A Bacillus coli was positive; for the other organisms, negative.

Control tests were carried out with strains of Bacillus typhosus, Bacillus paratyphosus, and certain negatively reacting Bacillus coli strains, and the reactions noted were end-reactions—tests with more highly diluted serum proving negative.

The macroscopic method, with fresh emulsions prepared after Borden's method, was used, and also fresh suspensions in 0.8 per cent. sodium chloride solution. October 21, the serum diluted 1 to 200 gave the same positive reaction against strain A Bacillus coli. October 23, the serum diluted 1 to 400 was positive for A. October 24, 26, and 28, serum diluted 1 to 200 was positive.

October 30 the serum was tested against strains A and B Bacillus coli and proved positive to strain A and negative to strain B, in dilution 1 to 200. November 1, the same reactions as on October 30 were obtained in dilutions of 1 to 100.

November 15, the serum diluted 1 to 100 was tested against 17 strains of Bacillus coli, including strains of A and B used previously.

The reactions were positive with strains 2, 6, 13, and A. December 29, the serum no longer agglutinated any of the Bacillus coli strains in dilutions of 1 to 100 and 1 to 20.

Bacillus coli strain A which constantly agglutinated with the serum diluted 1 to 100 from October 14 to November 15, and 1 to 400 October 23, had been obtained from one of the Bellevue cases above cited (1903). Strains 2, 6, and 13, which the serum, diluted 1 to 100, agglutinated November 15, had been obtained from the blood and the stool of a case of colon bacillus septicemia. Strain 6 was obtained from the ureter of a case of pyelitis. Therefore the serum of G. K. agglutinated 4 strains of Bacillus coli obtained from three different individuals.

For the various strains of Bacillus coli and Bacillus paratyphosus we were indebted to the laboratories of Drs. Buxton and Elser.

In connection with the study of Case III we have made numerous tests of the serum reactions of non-icteric and icteric cases.

NON-ICTERIC CASES. During the typhoid seasons of 1905, 1906, and 1907, 100 serum tests on 54 cases were carried out against Bacillus coli (strains A, B, and 2) and Bacillus paratyphosus (strains A and B).

The serum of a normal individual, used as a control, and the sera from 52 febrile cases, many of them Bacillus typhosus infections, were found negative to Bacillus coli (strain A) in dilutions above 1 to 20, with one exception. The serum from one febrile case, diluted 1 to 20, agglutinated Bacillus coli (strain A), and the serum from two cases, diluted 1 to 20, agglutinated Bacillus paratyphosus strains, but did not agglutinate Bacillus typhosus or Bacillus coli strains.

The sera from 31 cases did not agglutinate any one of several strains of the typhoid-colon group.

The sera from 16 cases agglutinated Bacillus typhosus, but not Bacillus paratyphosus and Bacillus coli strains.

Unfortunately, in 40 cases single tests only were made: In 6 cases two tests; in 3 cases three tests; in 1 case four tests; in 1 case six tests; in 2 cases nine tests; in 1 case ten tests; in the cases with six, nine, and ten tests the blood was taken at intervals extending over an entire month.

CASES WITH JAUNDICE AS A SYMPTOM. The sera of 13 cases with well-marked jaundice as a symptom were tested against strains of Bacillus typhosus and Bacillus coli—single observations in 12 cases and three observations in 1 case. In one instance, a single observation, Bacillus typhosus was promptly agglutinated both microscopically and macroscopically; in a second instance, Bacillus coli (strain B from a pleural exudate) was agglutinated macroscopically in dilution of 1 to 100, but not above; in a third instance, a case of catarrhal jaundice, Bacillus coli (strain 2) was agglutinated with serum diluted as high as 1 to 100.

Thus, none of these cases, with or without jaundice, agglutinated any one of the typhoid-colon group which were tested in dilutions above 1 to 100. In view of the fact that the sera from three jaundice cases were not tested over a period of weeks, we do not intend to discuss these single positive reactions as evidence that a particular strain of Bacillus coli was the infecting agent, although Kelly's paper suggests that such reactions may be of value in this direction.

For Bacillus typhosus it is well known experimentally that the sera of immunized animals must be diluted to the thousands before selective reactions are obtained, while in clinical medicine dilutions of the patients' sera 1 to 50 give diagnostic reactions within certain time limits.

In discussing the agglutination tests for the purpose of diagnosticating a colon bacillus infection, the following types of cases must be considered from theoretical and practical standpoints:

A. Cases of undoubted colon-group infection, in which blood cultures were positive during life and not during the pre-lethal stage or post-mortem. These cases may be divided into two groups:

1 (*a*) Cases which were typhoid-like in course, whose blood contained agglutinins for strains of the colon bacillus.

(*b*) Cases which were typhoid-like, whose blood did not contain agglutinins for strains of Bacillus coli.

2 (*a*) Cases which were not typhoid-like in course, whose blood contained agglutinins for strains of Bacillus coli.

(*b*) Cases which were not typhoid-like in course, whose blood did not contain agglutinins for strains of Bacillus coli. Endocarditis and pyelitis are examples of the last two groups.

B. Cases of supposed colon-group infection, with negative blood cultures. These cases likewise may be divided into two groups:

1. Cases which were typhoid-like in course, whose blood contained agglutinins for strains of Bacillus coli.

2. Cases which were not typhoid-like in course, whose blood contained agglutinins for strains of Bacillus coli. Cholecystitis and pyelitis are examples of this last group.

In the light of our knowledge of group-agglutinins, one must consider the relation of other typhoid-colon group infections to infections by the colon bacillus; for example:

1. Cases of undoubted Bacillus typhosus infection, clinically typhoid-like in nature, in which blood cultures and agglutination tests for Bacillus typhosus were positive and agglutinins for colon strains were found.
2. Cases in which agglutinins were positive for Bacillus typhosus alone, with blood cultures positive for Bacillus coli; or in which blood cultures were negative, and yet agglutinins were found for both typhoid and coli strains.
3. Cases in which blood cultures were positive for Bacillus paratyphosus and agglutinins were found for paratyphoid and colon strains.
4. Cases in which blood cultures were positive for Bacillus coli and whose serum agglutinated typhoid or paratyphoid strains.

Finally, the agglutination of colon strains by normal sera must be considered. The results of Klieneberger show a high agglutinin content for normal serum, diluted 1 to 2000 to 3000, for certain colon strains, and would lead one to consider the possibility that some individuals are producers of antibodies for Bacillus coli. Our results are at variance with Klieneberger's in that normal serum and sera from febrile cases have not caused agglutination of colon strains excepting in dilution of 1 to 20 in a febrile case without jaundice, and in dilution of 1 to 100 in two cases with jaundice. This contradiction is readily explained by the fact that in testing 17 different strains of Bacillus coli we found 4 strains only which were agglutinated by 5 out of 67 sera.

The fact that Klieneberger worked with a strain which was agglutinated by many normal sera would not invalidate our results unless it were proved that his colon strain is identical with one or more of those used by us.

Terminal colon bacillus infections and the reactions of typhoid bacillus carriers do not concern us.

Articles in the literature dealing with agglutination tests in Bacillus coli infections are not numerous, yet one or two of them, together with the results obtained in Case III cover the theoretical and practical considerations in respect to diagnostic reactions.

Klieneberger refers to Pfaundler's statement that the colon bacillus is agglutinated when one mixes together the serum and a strain of Bacillus coli obtained from the same patient, and not when the serum and bacteria are obtained from different individuals under normal conditions. From the work of Wassermann and others it is known that immune coli sera differ not only in respect to the strain used for immunizing, but also according to the type of animal used for immunization, and to explain these differences extensive variation in receptors of different coli strains are supposed to exist. Noting these statements, Klieneberger worked with sera from normal adults, and then from the newborn, with immune coli sera from immunized animals and from a man infected with Bacillus coli. The standard strain of Bacillus coli used was from the urine of a patient with a genito-urinary colon bacillus infection. Thirteen other strains of Bacillus coli were selected from 21 strains, for carrying out absorption experiments on sera agglutinating the standard strain. From six newborn infants, the sera being tested against 6 coli strains, 2 sera agglutinated 2 different strains, one each as high as 1 to 160; and the agglutination from 1 strain only was proved by absorption tests. From normal adults with no history of icterus or typhoid fever, 2 sera, diluted 1 to 1280, agglutinated 2 strains of Bacillus coli; 4 cases, 1 to 320, agglutinated 3 strains; 1 case, 1 to 640, agglutinated 1 strain. It is noticeable that 2 strains were agglutinated by 5 sera diluted 1 to 320 or over, and that each serum, 1 to 320, agglutinated at least 1 strain. Three strains were not agglutinated by any serum, and 5 strains were not agglutinated by any serum diluted above 1 to 80. No serum agglutinated Bacillus typhosus or Bacillus paratyphosus (A and B) above 1 to 20. One normal serum (M) agglutinated weakly 2 strains, with serum dilutions of 1 to 2560; 1 strain, with serum dilutions 1 to 640; 1 strain, 1 to 320; 1 strain, 1 to 160; and 3 strains not above 1 to 40. With normal serum M, by precipitation with 8 strains, partial agglutinins were found for 5 colon strains, and with normal serum R, partial agglutinins for 4 colon strains were found; and, further, it was found that one could group the agglutinable strains under two subdivisions, one of which was agglutinated constantly by highly diluted sera and the other irregularly and by low dilution. A second group of coli strains was not agglutinated by any serum. From these observations Klieneberger concludes that a tested strain of Bacillus coli has set up a specific immunity only when we can show that it is agglutinated with abnormally high dilutions, or that normal serum does not agglutinate the strain. He also speaks of an increment in agglutinating power as indicative of immunization from active infection, and cites 2 cases as showing this fact; and he refers to observations on Bacillus coli infections of the urinary tract, during which he had noted the same incremental auto-immunization.

In opposition to Pfaundler, the first fact noted was that in many Bacillus coli infections an agglutinating effect for the causative strain was absolutely wanting. He obtained a "group" agglutination for the typhoid bacillus four times, and for the paratyphoid bacillus once, with the Bacillus coli serum. Klieneberger concludes that in cases of Bacillus coli infection in man, when the causative agent has not been isolated, it is scarcely possible to prove a Bacillus coli infection with serum tests unless immunity to Bacillus coli can be determined, when an increasing agglutination and abnormally high agglutination is found, and normal controls are negative. Further, Klieneberger immunized rabbits against 5 active strains of Bacillus coli with 1 c.c. of a formalized broth culture injected intravenously and obtained a high agglutinating power against the immunizing strain and a much less ($\frac{1}{10}$ of the high) agglutinating power against 3 non-immunizing strains, and negative results against 8 other Bacillus coli strains, 1 typhoid strain, and paratyphoid strains A and B. A similar chief agglutinin was obtained with the 5 strains used for active immunization.

Case III (G. K.) illustrates well the increment of agglutination which is essential, according to Klieneberger, for the proof of Bacillus coli immunization.

Mayer found one strain (R) which was usually agglutinated by normal serum diluted 1 to 100 (macroscopic test) and 1 to 250 (microscopic test), and other strains (M, N, L) with which agglutination was not obtained with sera little diluted. Strain M not only did not agglutinate well with normal serum, but was not readily agglutinated by serum (1 to 50) from an animal immunized to strain R, and did not produce agglutinins of any power when used for immunization.

This variation in the agglutinability and in the antigen for agglutinin in certain strains was the most interesting result of Mayer's investigation. Dead bacteria (Bacillus coli, twenty-hour cultures) gave stronger agglutinins and with more certainty than living bacteria when used for immunizing animals, an observation also made by Radzievsky (1900).

Bauermeister's case of general Bacillus coli infection, and later abscess of the testicle, was not carefully studied for agglutinins. An organism isolated from the abscess gave a "Widal" (?) 1 to 50, while the bacilli (Bacillus coli) from the blood and from the urine were not agglutinated; whether with the patient's serum or not does not seem clear. The bacillus isolated from the abscess—one and one-half years after the observations on the blood and urine—did not present the same cultural characteristics as those of the bacilli isolated from the urine and blood.

Jochmann, in 1906, recorded some interesting observations on infections of the urinary tract and general infection with the colon bacillus—two cases with an intermittent fever. In one case, following operation for carcinoma of bladder and subsequent catheterization, pneumonic signs developed, and later chills occurred, after which blood cultures with 20 c.c. of blood gave a growth of 10 colonies of Bacillus coli. In a second case, during a cystitis due to Bacillus coli, 8 colonies of Bacillus coli were grown from 20 c.c. of blood. Jochmann considered both these cases a blood invasion by Bacillus coli. In the first case Jochmann tested the agglutinating power of the serum against Bacillus typhosus, Bacillus paratyphosus, and several Bacillus coli strains. No reactions were obtained with Bacillus typhosus and Bacillus paratyphosus, and one strain of Bacillus coli was agglutinated by serum diluted 1 to 80, and the

Bacillus coli isolated from the patient was agglutinated by serum diluted 1 to 160. The patient's strain of Bacillus coli was agglutinated also by sera diluted 1 to 80 from four cases of acute cholelithiasis and by serum, diluted 1 to 320, from a protracted case of cholelithiasis; and a case of icterus with hepatic conditions and cholangitis gave a serum which, diluted 1 to 160, agglutinated the same strain of Bacillus coli. These cases he considered Bacillus coli infections. Jochmann tried 8 normal sera against the Bacillus coli strain from his Case I, and obtained reactions with dilutions no higher than 1 to 40. He thought a reaction with serum diluted 1 to 80 necessary to indicate infection with Bacillus coli, and that the reaction would be of value when no group agglutinins for Bacilli typhosus and paratyphosus were obtained. If the latter were present, one might still obtain a specific Bacillus coli reaction by saturating the sera (by absorption) after Castellani's method. Later, Jochmann tested the sera of 16 other Bacillus coli infections and obtained reactions with highly (?) diluted serum, so that he disagreed with Köhler and Scheffler, who claimed that such reactions are of no value. Jochmann also concluded that the homologous strain would agglutinate with more highly diluted sera than the heterologous strains, as stated by Pfaundler, which is contrary to the experience of Klieneberger and to our results.

Fehling's article deals mainly with infections of the genito-urinary tract during pregnancy and the puerperium. In one case of pyelonephritis in pregnancy, with fever for the fourteen days *ante partum* and at delivery, cultures from the blood were sterile; and cultures from the fœtus were sterile. The fever disappeared on the fourth day of the puerperium, and the bacteruria persisted. Fourteen days after delivery the mother's blood, diluted 1 to 150, agglutinated a bacillus (Bacillus coli) isolated from the urine. He concluded that the Bacillus coli was in the mother's blood at the same time, admitting the possibility of agglutinating substance coming from the fœtus through the placenta. From another case, following an obstetrical operation, he obtained Bacillus coli from the blood, urine, sputum, and sweat, and this case he considered the eighth of pure Bacillus coli sepsis recorded in the literature. No agglutination tests were carried out.

The nosological position to be given to the typhoid-like cases caused by Bacillus coli communis demands brief consideration. As in the case of typhoid-like infections by the intermediate members of the Typhaceæ, it is impossible to differentiate these cases from infections by Bacillus typhosus by clinical methods alone. The assistance of the laboratory is required. Before the development of exact bacteriological diagnosis, all typhoid-like cases, by whatever member of the group they were caused, were considered as typhoid fever. The diagnosis was based necessarily upon clinical data. Since the discovery that the symptom-complex of typhoid fever may be caused by several members of the Typhaceæ, the nosological position of these cases has been under discussion.

Two courses are open to us: to classify the cases clinically or bacteriologically. The former course is the simpler, and is followed in the case of many other diseases. Classification on a bacteriological basis necessitates the introduction of a separate term for each variety of infection. Therefore, we are inclined to advocate the classification of all cases of infection by the Typhaceæ, *when they pursue a typhoid-like course,* as clinical typhoid fever.

CONCLUSIONS. 1. Isolated reactions against Bacillus coli are without significance in respect to the cause of infection.

2. The blood serum of a case of infection by Bacillus coli communis may contain agglutinins for certain strains of this group while the infection persists and not upon the patient's return to health.

3. The detection of an increment of agglutinins in the blood serum for a particular strain of Bacillus coli communis is evidence of a local or general infection with that strain.

4. Some strains of Bacillus coli communis are capable of causing a disease clinically identical with typhoid fever.

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For other references to colon bacillus sepsis, see Jochmann's paper.